## ***Remarks***

Claims 26-28 are pending in the application. No claims were amended. The Applicants expressly reserve the right to further prosecute the same or similar claims in subsequent patent applications claiming the benefit of priority to the instant application. 35 USC § 120.

## ***Claim Rejections Based on 35 USC § 103(a)***

Claims 26-28 were rejected under 35 USC 103(a), based on the Examiner's contentions that they are unpatentable over various patents and publications. To better organize the Applicant's traverses of the Examiner's rejections under 35 USC 103(a), they are set forth below in paragraphs numbered corresponding to the numbering scheme used in the Office Action.

2. Claims 26-28 were rejected under 35 USC 103(a), based on the Examiner's contention that they are unpatentable over WO 92/02256. Specifically, the Examiner contends that "it is deemed obvious to one of ordinary skill in the art to encapsulate fentanyl or any compound based on the basic structure of fentanyl in the cyclodextrin compositions of WO with a reasonable expectation of success." The Applicants traverse on ground that WO 92/02256 does not teach all the limitations of the rejected claims. Moreover, the Applicants respectfully urge that the Examiner has failed to introduce into the record any suggestion or motivation to modify the teachings of WO 92/02256 for oral administration.

First, the Applicants respectfully contend that WO 92/02256 does not form the basis of a proper 35 USC § 103(a) rejection because WO 92/02256 does not teach all of the limitations of the claims. Specifically, WO 92/02256 does not teach the limitation of claim 26 that the formulation is administered orally. The Examiner has already stated in the Office communication dated October 21, 2004 that WO 92/02256 does not teach oral administration. The Applicants respectfully remind the Examiner that in order "to establish a *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." *MPEP* 2143.03. *See also In re Royka*, 490 F.2d 981.

Second, the Applicants respectfully contend that WO 92/02256 does not form the basis of a proper 35 USC § 103(a) rejection because there is no suggestion or motivation to modify

WO 92/02256 for oral administration. The Applicants point out that the intended purpose of the invention in WO 92/02256 is to limit distribution of the drug to the neuraxis of a patient, i.e., the drug is to be prevented from dispersing throughout the body, such as by migration via the circulatory system. *See* WO 92/02256, page 1, line 27 through page 2, line 21. WO 92/02256 states "a key goal of the present invention has been to develop improved methods that will allow the routine, acute and chronic administration of agents into the neuraxis via intraventricular, epidural, intrathecal, intracisternal and related routes." *See* WO 92/02256 page 2, lines 11-14.

In stark contrast to the intended purpose of the invention in WO 92/02256, the instant claims are directed to oral administration of the pharmaceutical agent. Critically, after being absorbed through the intestinal wall orally administered formulations are distributed throughout the body via the circulatory system. *Hence, modifying WO 92/02256 for oral administration would render it unsatisfactory for its intended purpose of limiting distribution of the drug.* The Applicants respectfully remind the Examiner that "if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *See In re Gordon*, 733 F.2d 900, 221 USPQ 1125, (Fed. Cir. 1984).

From another standpoint, the Applicants again contend there is no suggestion or motivation to modify WO 92/02256 for oral administration because WO 92/02256 does not suggest the desirability of oral administration. WO 92/02256 teaches that widespread distribution of centrally acting drugs causes serious side effects and should be avoided. *See* WO 92/02256, page 1, line 27 through page 2, line 10. Oral administration, in contrast, leads to widespread distribution of the pharmaceutical agent. Hence, WO 92/02256 does not suggest the desirability of oral administration. The Applicants respectfully remind the Examiner that "the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *See In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Moreover, the Examiner has failed to introduce on the record a second reference to be combined with WO 92/02256.

*Regarding the Examiner's inquiry as to the dose of fentanyl administered in Example 1, the Applicants point out that the second paragraph of Example 1 states the dose was 0.05 mg/kg*

*at each time point.* The first sentence of the first paragraph states the rats weighed 150-200 grams. Hence, the fentanyl dose at each time point ranged from 7.5 μg -10 μg depending on the weight of the rat.

Irrespective of the suggestion for additional studies in the Shaiova abstract, the Applicants also contend that there has been a long-felt need for oral formulations of fentanyl. As described in Applicant's communication dated June 18, 2004, fentanyl formulations have been known since the 1960s, and yet ACTIQ® is the only known FDA-approved oral formulation of fentanyl. However, ACTIQ®, a transmucosal formulation of fentanyl citrate, is not satisfactory because it causes nausea, vomiting, and/or a burning sensation in the mouth. Importantly, the present invention fulfills the long-felt need for a fentanyl formulation that can be administered orally. The Applicants respectfully remind the Examiner that a long-felt need is one of the secondary considerations that must be considered in a assessment of nonobviousness. *See* MPEP § 2141.

Finally, the Applicants respectfully remind the Examiner that "a determination under 35 USC 103(a) should rest on all the evidence and should not be influenced by any earlier conclusion." *See In re Lilly & Co.*, 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990); and MPEP § 2144.08. Specifically, the Applicants are concerned that the Examiner is reluctant to re-examine, in light of new evidence and attorney argument, conclusions reached earlier during prosecution of the instant application.

Accordingly, the Applicants respectfully request the withdrawal of the rejections of claims 26-28 under 35 USC 103(a) based on WO 92/02256.

4. Claims 26-28 were rejected under 35 USC 103(a), based on the Examiner's contention that they are unpatentable over WO 00/47203. The Examiner states that WO 00/47203 "teaches formulations containing narcotic analgesics such as fentanyl citrate in combination with hydroxypropyl-beta cyclodextrin for oral administration." Furthermore, the Examiner contends that "it would have been obvious to one of ordinary skill in the art to use any fentanyl based compound with hydroxypropyl-beta cyclodextrin, with a reasonable expectation of success since it is a[n] absorption enhancer." The Applicants respectfully traverse.

The Applicants respectfully contend that WO 00/47203 does not form the basis of a proper 35 USC § 103(a) rejection because one of ordinary skill in the art would have no reasonable expectation of success in enhancing the efficacy of fentanyl by adding a cyclodextrin based on WO 00/47203. As stated by the Examiner in the Office communication dated October 21, 2004, there are no examples in WO 00/47203 of using fentanyl citrate in combination with hydroxypropyl-beta cyclodextrin. Example 6 is the only working example comprising fentanyl citrate, and this example does not specify the identity of the absorption enhancer. Moreover, example 6 does not provide control data to determine if the "absorption enhancer" is actually enhancing absorption. The data in example 6 of WO 00/47203 only indicate that some effect on rats 636 and 637 was observed when the formulation was administered via pipette. *However, the mere observance of an analgesic effect provides no evidence of enhanced absorption because, as the Applicants have shown on page 45 of the instant application, oral administration of fentanyl alone produces a mild analgesic effect.*

It is also worth noting that administration of fentanyl citrate with the "absorption enhancer" in example 6 of WO 00/47203 produced no effect at all on rats 632, 633, and 634. *See* Tables 1 and 2 in example 6. Therefore, the Applicants contend that based on teachings and examples in WO 00/47203 one of ordinary skill in the art would have no reasonable expectation of success in enhancing the efficacy of fentanyl by adding a cyclodextrin.

In addition, Applicants contend that claims 26-28 are not obvious because the invention satisfies a long-felt need as described above in connection with the traverse of the rejection based on WO 92/02256. The Applicants respectfully remind the Examiner that a long-felt need is one of the secondary considerations that must be considered in a determination of obviousness. *See* MPEP § 2141.

Finally, the Applicants respectfully remind the Examiner that "a determination under 35 USC 103(a) should rest on all the evidence and should not be influenced by any earlier conclusion." *See In re Lilly & Co.*, 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990) and MPEP § 2144.08. Specifically, the Applicants are concerned that the Examiner is reluctant to re-examine, in light of new evidence and attorney argument, conclusions reached earlier during prosecution of the instant application.

Accordingly, the Applicants respectfully request the withdrawal of the rejections of claims 26-28 under 35 USC 103(a) based on WO 00/47203.

5. Claims 26-28 were rejected under 35 USC 103(a), based on the Examiner's contention that they are unpatentable over WO 92/02256 in view of Farrar et al. (JNCI, 1998), Portenoy et al. (Pain, 1999), and Stanley et al. (Anesth. Analg. 1989). The Examiner states that the Farrar, Portenoy, and Stanley references each teach the efficacy of fentanyl when administered orally. Furthermore, the Examiner contends that "oral administration of the compositions of fentanyl based compounds, with a reasonable expectation of success would have been obvious to one of ordinary skill in the [art] since the references of Farrar et al., Porenoy et al., [and] Stanley et al. show the efficacy of orally administered fentanyl." The Applicants respectfully traverse.

The Applicants respectfully contend that WO 92/02256 in view of Farrar et al. (JNCI, 1998), Portenoy et al. (Pain, 1999), and Stanley et al. (Anesth. Analg. 1989) does not form the basis of a proper 35 USC § 103(a) rejection because it is improper to combine WO 92/02256 with Farrar et al., Portenoy et al., or Stanley et al. In support of this conclusion, the Applicants respectfully remind the Examiner that "it is improper to combine references where the references teach away from their combination." *See In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983) and MPEP § 2146. As discussed above, the Applicants contend that WO 92/02256 teaches that the distribution of the drug is to be strictly limited to the neuraxis of a patient, i.e., the drug is to be prevented from dispersing throughout the body such as by migration via the circulatory system. *See* WO 92/02256, page 1, line 27 through page 2, line 21. WO 92/02256 teaches "this vascular redistribution clearly results in powerful and acute supraspinal side effects. Such side effects are often serious and sometimes fatal." *See* WO 92/02256, page 2, line 9-10. In contrast to the teachings of WO 92/02256, the disclosures of Farrar et al., Portenoy et al., and Stanley et al. teach oral administration of fentanyl citrate which leads to widespread distribution of the drug throughout the body. For example, Farrar et al. teaches a lozenge comprising fentanyl citrate that dissolves in the mouth, whereby the fentanyl is absorbed through oral muscosa. *See* Farrar et al., pages 611-12. Once absorbed, the fentanyl is dispersed throughout the entire body by the circulatory system. Hence, it is improper to combine WO

92/02256 with Farrar et al., Portenoy et al., or Stanley et al. because WO 92/02256 teaches away from methods of administration, such as oral administration, that lead to widespread distribution of the drug throughout the body.

In addition, Applicants contend that claims 26-28 are not obvious because the invention satisfies a long-felt need as described above with respect to rejection based on WO 92/02256. The Applicants respectfully remind the Examiner that a long-felt need is one of the secondary considerations that must be considered in a determination of obviousness. *See* MPEP § 2141.

Finally, the Applicants respectfully remind the Examiner that "a determination under 35 USC 103(a) should rest on all the evidence and should not be influenced by any earlier conclusion." *See In re Lilly & Co.*, 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990) and MPEP § 2144.08. Specifically, the Applicants are concerned that the Examiner is reluctant to re-examine, in light of new evidence and attorney argument, conclusions reached earlier during prosecution of the instant application.

Accordingly, the Applicants respectfully request the withdrawal of the rejections of claims 26-28 under 35 USC 103(a) based on that WO 92/02256 in view of Farrar et al. (JNCI, 1998), Portenoy et al. (Pain, 1999), and Stanley et al. (Anesth. Analg. 1989).

## *Fees*

The Applicants believe no required fees are required in connection with the filing of this paper. Nevertheless, the Director is hereby authorized to charge any required fee to our Deposit Account, **06-1448**.

## Conclusion

In view of the above amendments and remarks, it is believed that the pending claims are in condition for allowance. The Applicants respectfully request reconsideration and withdrawal of the pending rejections. The Applicants thank the Examiner for careful consideration of the present case. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to contact the undersigned.

Respectfully submitted,
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